Schwartz S, Etropolski M, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27:151-162.

Design: Randomized clinical trial

Population/sample size/setting:

- 585 patients (341 men, 244 women , mean age 61) who participated in a clinical trial of extended release tapentadol in Germany and the USA
- Eligibility requirements were painful diabetic peripheral neuropathy (DPN) for at least 6 months, HbA1c <=11%, at least 3 months of unsatisfactory analgesic use for DPN (<=160 mg oral morphine equivalent if using opioid), and average pain intensity at least 5 on a scale from 0 to 11
- Exclusion criteria were participation in another tapentadol trial, history of alcohol and/or drug abuse, a condition other than DPN that could confound the evaluation of pain response (fibromyalgia, RA), and several significant medical comorbidities that could compromise safety
- Use of SSRI was allowed, as was rescue medication with low dose tapentadol; other medication use was prohibited during the study period

Main outcome measures:

- The study was divided into 2 phases: a 3 week open-label phase and a 12 week double-blind phase
- All 585 patients entered the open-label phase, during which their tapentadol dose was titrated to an individually optimal dose, beginning at 50 mg bid for 3 days, then titrated to a minimum dose of 100 mg bid and a maximum dose of 250 mg bid; acetaminophen up to 2 g was allowed as additional analgesia, except during the last 4 days
- After the open-label phase, only those patients (n=389) with at least a 1 point improvement in pain scores entered the double blind phase of the study
- The 389 patients who entered the double-blind phase were randomized to continued treatment with an unchanged dose of tapentadol (n=196) or to an identical-appearing placebo (n=193)
- In the placebo group, tapentadol 100 mg bid was given for the first 3 days to minimize withdrawal symptoms; after the first 4 days, a single daily 25 mg dose of tapentadol was allowed as supplemental analgesia in both groups
- Multiple outcomes were measured; the principal outcome was the change in pain scores from baseline to the end of the double-blind phase of the study, but patient global impression of change (PGIC) was also recorded
- 196 patients who entered the open-label phase discontinued before starting the double-blind phase; 100 of these were for adverse events, and 23 for lack of efficacy; these represented one third of the study population
- The mean pain intensity at the beginning of the open-label phase was 7.3; at the beginning of the double-blind phase, the mean pain intensity was 3.5
- During the double-blind phase, attrition was equal in the tapentadol group (n=63) and the placebo group (n=62)

- The reasons for discontinuation were different in the two groups; in the tapentadol group, 29 were for adverse events and 8 for lack of efficacy; in the placebo group, 15 were for adverse events and 29 for lack of efficacy
- In the tapentadol group, there was no change in average pain intensity during the double-blind phase, but in the placebo group, there was an increase in average pain intensity of 1.4 points on the 0-10 pain score scale
- For the PGIC, 64.4% of tapentadol patients reported being "much improved" of "very much improved;" but this was reported by only 38.4% of placebo patients
- The most common adverse effects were nausea, dizziness, somnolence, constipation, vomiting, fatigue, headache, and pruritus; most were mild to moderate in intensity

Authors' conclusions:

- Tapentadol ER is effective and well-tolerated in patients with chronic neuropathic pain associated with diabetes
- Although opiate withdrawal symptoms were not commonly recorded, patients who were randomized to placebo may have been able to detect their randomization to placebo; since unblinding questionnaires were not used, some patients may have been unblinded

Comments:

- The enriched enrollment design (randomizing only patients who responded to and tolerated the drug in the open-label phase) is a generally acceptable method of evaluating analgesic drugs
- The double-blind phase of an enriched enrollment study can be conceived as a way of demonstrating that the responders in the open-label phase were responding to something other than placebo; loss of therapeutic response, which was used in this study, is a generally accepted outcome
- As the authors concede, the potential for unblinding in the double-blind phase of the trial could not be assessed because there was no questionnaire
- Most of the attrition during the titration phase was due to adverse effects, not due to lack of analgesic effect; dose titration may be a difficult aspect of the use of tapentadol in clinical practice

Assessment: Adequate for evidence that tapentadol may alleviate neuropathic pain with tolerable adverse effects